IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Gregory H. Altman et al.	Confirmation No.:	6963
Application No.:	10/800,134	Group No.:	1657
Filed:	December 15, 2003	Examiner:	David M. Naff
For:	IMMUNONEUTRAL SILK-FIBER-BASED MEDICAL DEVICES		

DECLARATION OF DAVID KAPLAN, PH.D. UNDER 37 C.F.R. 1.132

I, David Kaplan, Ph.D., pursuant to 37 C.F.R. § 1.132, hereby declare that:

1. I am currently employed as a Professor and Chair of the Department of Biomedical Engineering at Tufts University. I am also a Professor in the Department of Chemical & Biological Engineering; Director of the Bioengineering & Biotechnology Center; and Director of the Tissue Engineering Resource Center, all at Tufts University.

2. I have authored or co-authored over 350 peer-reviewed publications. Many of the publications involve tissue engineering, silk, and silk-based medical devices. I have over thirty years experience in the field of Natural Biomaterials.

3. A copy of my *Curriculum Vitæ* is attached.

4. I have reviewed the Final Office Action issued May 2, 2007 by the United States Patent and Trademark Office ("PTO") on Invention and the cited U.S. Patent Nos. 6,303,136 (Li); 7,014,807 (O'Brien); 5,994,099 (Lewis); and 5,736,399 (Takezawa).

5. The Office Action contains the following statement:

> "It would have been obvious to use as the filamentous matrix of Li et al. a yarn produced from fibrion fibers from which sericin had been removed as

> disclosed by O'Brien in view of Lewis et al. suggesting preparing a matrix for tissue reconstruction from silk and Takezawa et al. using a silk mesh as a culture carrier. ... Not dissolving as disclosed by O'Brien would have been obvious when dissolving is not desired."

That statement is incorrect, in view of the state of the art as of the filing date of Invention. One skilled in the art would not have made the combination as of the filing date for the following reasons.

6. The device of Li has a non-degradable filamentous matrix surrounded by a semipermeable membrane. The device of Li requires the use of non-degradable fibers and that the use of degradable fibers would render the device of Li inoperable. The device of Li requires the use of non-degradable fibers that do not release by-products into the host. Li specifically mentions suture silk as an example of a non-degradable fiber suitable for use in the device. Li consistently describes the fibers used as being non-degradable or substantially non-degradable starting from the title and continuing throughout the specification and claims. It is my opinion that Li does not teach using sericin-extracted fibroin fibers. The device of Li requires the use of non-degradable fibers and that the use of degradable fibers would render the device of Li inoperable. Li teaches away from the present invention by teaching the matrix be made from "substantially non-degradable" fibers (Li, Col. 3, line 1). Li teaches that degradation would render the invention inoperable: "A "biocompatible capsule" is a capsule that, upon implantation in a host mammal, does not elicit a detrimental host response sufficient to result in the rejection of the capsule or to render it inoperable, such as through degradation." (Li, Col. 6, lines 43-46, emphasis added).

7. O'Brien discloses the production of regenerated polypeptide fiber. O'Brien teaches regeneration of decrystallized polypeptide by dissolving the silk protein, reconstituting it in solution, and re-spinning it to produce fiber threadline (O'Brien, Col. 3, line 50-64). O'Brien requires dissolving and reconstituting the native silk proteins and requires "decrystallized" silk flake to practice the teaching. See O'Brien, Col. 3, Line 50-57 and

Claim 1. O'Brien does not provide an option to dissolve or not to dissolve the silk fibroin but requires dissolving.

8. Accordingly, there was no reason apparent to one skilled in the art to make the suggested combination. In fact, without further processing, the regenerated polypeptide fiber of O'Brien would be degradable and therefore, O'Brien teaches away from the combination of the references. In my opinion, one of ordinary skill in the art would not have had a reasonable expectation of success in combining the references.

9. Furthermore, the sericin-extracted, dissolved and reconstituted silk fibers produced by the method of O'Brien differ from the sericin-extracted fibroin fibers of the present invention that retain their native protein structure and have not been dissolved and reconstituted. The properties of dissolved and reconstituted fibers (also known as regenerated silk fibroin) have been shown to differ significantly from native silk fibroin (which have not been dissolved and reconstituted). See Zou, B., et al., *J. Mater. Sci.*, 41: 3357-3361 (2006) and Xie, F., et al., *Internat. J. Biolog. Macromol.*, 38: 284-288 (2006), attached as Exhibits A and B.

10. The fibers produced by the decrystallization and reconstitution process of O'Brien differ significantly from the fibers of the present invention in their physical and mechanical properties. The fibers produced from the reconstituted protein are composed of sections of polymer of variable length. See O'Brien, Col. 1, Lines 13-24. The polymer sections overlap to various extents and may or may not be oriented parallel to the axis of the fiber. Also, the numerous chain ends of the polymer sections act as defects that substantially limit fiber tensile strength. Conversely, the fibers of the present invention are essentially unbroken polymer chains without the attendant deficiencies described above.

11. O'Brien teaches that if the chain lengths are too short the chain ends act as defects resulting in brittle fibers. And that it is preferred to have the highest average chain length possible. (O'Brien, Col. 1, Lines 16-24) With this in mind, O'Brien still requires

dissolving and reconstituting the native silk proteins and requires "decrystallized" silk flake to practice the teaching. (O'Brien, Col. 3, Line 50-57 and Claim 1) The difference between fibers that are each made up of an essentially unbroken polymer as in the present invention and the properties inherent in such a fiber must be contrasted with fibers produced from decrystallized polymer. The properties of dissolved and reconstituted fibers (also known as regenerated silk fibroin) have been shown to differ significantly from native silk fibroin (which have not been dissolved and reconstituted). See Zou, B., et al., *J. Mater. Sci.*, 41: 3357-3361 (2006) and Xie, F., et al., *Internat. J. Biolog. Macromol.*, 38: 284-288 (2006), attached as Exhibits A and B. The decrystallized/reconstituted protein results in short sections of polymer of various orientations and the attendant disruption and change of mechanical properties. Native and decrystallized polymers are no more comparable than a piece of wood (native) is to a piece of paper (reconstituted).

12. It is my expert opinion that O'Brien provides no suggestion or motivation to use sericin-extracted fibroin fibers that retain their native protein structure and have not been dissolved and reconstituted as required by the present claims.

13. Lewis teaches cloned DNA encoding spider flagelliform silk protein. Lewis describes spider-silk fibers formed by extrusion of liquid-crystal solutions as in the method of O'Brien. As in O'Brien, Lewis teaches formation of fibers from dissolved protein (Lewis, Col. 20, line 37).

14. The fibers produced by the decrystallization and reconstitution process of Lewis differ significantly from the fibers of the present Invention in their physical and mechanical properties as mentioned in paragraph 10 above, concerning the fibers of O'Brien.

15. The Office Action contains the following statement:

> "It would have been obvious to use as the filamentous matrix of Li et al. a yarn produced from fibrion fibers from which sericin had been removed as disclosed by O'Brien in view of Lewis et al. suggesting preparing a matrix for tissue reconstruction from silk and Takezawa et al. using a silk mesh as a culture carrier. Such fibers will be degradable." (emphasis added)

One skilled in the art would recognize that such fibers would be degradable and, therefore, could not be used to make the filamentous matrix of Li. And that Li, by repeated insistence on use of non-degradable fibers, teaches away from the suggested combination of references. In my opinion, one of ordinary skill in the art would not have had a reasonable expectation of success in combining the references.

16. Takezawa describes a culture-carrier of natural or synthetic threads. The use of the degradable, dissolved and reconstituted silk fibers of O'Brien or Lewis would render the device of Takezawa inoperable. The use of degradable fibers would not achieve the intended advantage of "providing a novel culture carrier in which animal cells can proliferate three-dimensionally". As a result, Takezawa teaches away from the suggested combination of references.

17. In conclusion, I strongly disagree with the position of the PTO that the above references are combinable or that the combination would render claims 1, 2, and 4-31 of the above Application unpatentable. Contrary to the position of the PTO, for the reasons set forth above, it would not have been obvious to a skilled artisan to substitute a yarn produced from fibroin fibers from which the sericin has been removed as disclosed by O'Brien for the filamentous matrix of Li et al.

The teachings of Lewis and/or Takezawa do not alter my position. Lewis taught regenerated spider silk. As mentioned above, regenerated silk has different properties, such as lower strength, than natural silk fibroin. Takezawa taught a culture carrier. As noted above, Takezawa, like Li, would direct the skilled artisan to use of non-degradable fibers, as degradable fibers would render the device of Takezawa inoperable.

For these reasons set forth above, it is my expert opinion that the references cited by the PTO, alone or in combination, would not teach or suggest the claimed invention. The combination or modification of the prior art references in the manner suggested by the PTO was contrary to the accepted wisdom in the art at the time of Applicant's invention and, as discussed above, such combination would render the references inoperable for their intended purposes. One of ordinary skill in the art would not have had a reasonable expectation of success in combining the references suggested by the PTO.

Oct 29, 2007
Date

David Kaplan

Faculty Profiles

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Scholarship & Research:	Extracellular matrix remodeling – methods to quantify cell-matrix interactions. L.C. Abraham, J.F. Dice, P.F. Finn, N.T. Mesires, K. Lee, D.L. Kaplan. Biomaterials, 28: 151-161 (2007).

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